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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,076	WISE, CAROL A.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 41-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 43-59* is/are rejected.

7)☒ Claim(s) *41 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. The current application claims priority to 09/710,693 and to 60/287,893. While the provisional application, 60/287,893 provides descriptive support for the claims, no support for the G688A polymorphism was found in application 09/710,693. Consequently, priority is granted only until May 1, 2001, the filing date of the provisional application.

Claim Rejections - 35 USC § 112 – Written Description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 38, 43-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register:

December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

Claims 38, 43-46 and 53 encompass a genus of nucleic acids which are different from those disclosed in the specification. Specifically, claim 38 permits conservative, but undisclosed, amino acid variants, which would necessarily result in undisclosed nucleic acid variation. The genus is immense, since SEQ ID NO: 20 is 1428 nucleotides in length, and possible changes in even a few amino acids would result in literally hundreds of trillions of different possible species. This large genus is represented in the specification by only the particularly named SEQ ID Nos. Thus, applicant has express possession of only two substitutions and the wildtype in the gene. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims expressly encompasses allelic variations including insertions and deletions and is permissive of alternately spliced versions of the proteins, inactive precursor proteins which have a removable amino terminal end, while only specific amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

With regard to claims 47-52, these claims encompass the full length gene with conservative substitutions as above since the claims are of the open "comprising"

format. So while the claim indicates a size for the oligonucleotide, the use of the term "comprising" negates this as an upper bound to the nucleic acid molecule.

With regard to claims 54-59, the claim does not require that the sequence be "fully complementary".

Further, with regard to claim 53, no description of the hybridizing oligonucleotides is provided and this genus is also immense.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the "conservative variants" lacks any specific structure, and is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the two specific substitutions, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound without even the limitation of a functional utility, and without any definition of the particular conservative substitutions claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise substitutions or hybridizing oligonucleotides to SEQ ID NO: 20 or 22. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Response to Arguments – Written Description rejection

4. Applicant's arguments filed April 13, 2004 have been fully considered but they are not persuasive.

Applicant argues that the specification clearly describes, at paragraph 32 on page 12, conservative amino acid variants. This statement is not correct. The specification does not describe any specific variants at page 12, but rather simply discusses what constitutes a conservative variant. Further, Applicant's legal analysis of the MPEP is not consistent with the case law or with the claim. First, the case law clearly indicates that undescribed variation does not comply with the written description requirement. As the court noted in Fiers "if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred." Here, there is no detailed chemical structure of the "conservative variants", so it is clear that there is no conception of DNA sequences which code for these variants. Second, the claim is open to any number of conservative variants. So the claim would read on an entirely different protein. So using the table of conservative amino acid substitutions at page 12, paragraph 32, the first 10 amino acids of SEQ ID NO: 20, M M P Q L Q F K D A would encompass variations such as A A L S A S P R E L, since every amino acid changed was a "conservative variant". Applicant did not describe the second variation or any of the literally hundreds of trillions of other variations possible based upon the "conservative variant" language." This is not the case of a single point mutation mentioned in the MPEP 2144.08, where there are only 19 other possible amino acids which can be changed. Further, Applicant failed to include provide the complete quote from the MPEP, which concludes "Although at some locations a

conservative substitution may be benign, in some proteins only one amino acid is allowed

at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. (See MPEP 2144.08)." So the cited portion of the MPEP recognizes that even a very small change, of a single methyl group, can significant differentiate a protein. Here, where the claimed nucleic acid could literally encode an entirely different protein sequence, with no identical amino acids whatsoever to the disclosed protein, the claim clearly fails to comply with the written description requirement.

When Applicant then argues that only 20 nucleotides are required, this further broadens the claim, because the claim encompasses sequences not disclosed, suggested, or contemplated in any way by the Applicant. For example, the 30 nucleotide sequence which encodes the first 10 amino acids above is

atgatgccccagctgcagttcaaagatgcc, while one sequence for the "conservative variant" sequence given above is

gcagcattatccgcttctccgcgcgagcta

The sequences share only 2 nucleotides out of 30 in common (6% identity) and have a stretch of 24 nucleotides where there are literally no identical sequences. It is abundantly clear that this provides substantial evidence that Applicant was not in possession of either full length or of 20 nucleotide fragments with conservative variants, when there are 20 nucleotide regions which share ZERO homology with applicant's

sequence. In fact, it is extremely likely that there are longer stretches of zero percent homology, but this is a simple example where the first 10 amino acids were used.

Applicant concludes by arguing that the amendment to "differentially hybridize" overcomes the written description rejection on that claim. Once again, the genus is immense and Applicant does not have possession of more than a very few species in this immense genus. Further, in neither claim situation is there any function consonant with the written description guidelines. Consequently, this rejection is maintained.

Claim Rejections - 35 USC § 112 – Second paragraph

5. Claims 47-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "at least about 20 contiguous nucleotides". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 20 nucleotides are permitted. Further, the extent of variance permitted by "about" is unclear in this context. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The rejection of claims 38, 43-46 under 35 U.S.C. 102(b) as being anticipated by Hillman et al (WO 00/06728) is withdrawn in view of the amendment.

8. Claims 47-53 are rejected under 35 U.S.C. 102(e) as being anticipated by Fodor et al (U.S. Patent 6,582,908).

First, claim 47 must be interpreted with regard to the scope of the phrase "about 20 contiguous nucleotides". The phrase "about" permits some flexibility in the length of the oligonucleotide. Since the specification lacks any definition of the term "about", it is deemed to be a broad term which permits the 10-mer nucleic acids of Fodor to apply.

Fodor teaches an array of every possible 10-mer oligonucleotide (see column 22, lines 14-16). This 10-mer array inherently comprises every possible 10-mer, including 10-mers which are 100% complementary to the G688A mutation and the G748C mutation. Further, with regard to claims 48-51, the 10-mer array inherently comprises every orientation, with the nucleotide at the 3' end or at the 5' end, since some 10-mers will have the mutation at the 3' end and some will have the mutation at the 5' end. With regard to claim 52, some of the 10-mers will inherently comprise the complement of the oligonucleotide of claim 47. Finally, with regard to claim 53, many of the 10-mers will

hybridize to the nucleic acid molecule of claim 47 but will not hybridize to SEQ ID NO: 18 under appropriate hybridization conditions.

Response to Arguments – 35 U.S.C. 102 rejection

9. Applicant's arguments filed April 13, 2004 have been fully considered but they are not persuasive.

Applicant's arguments were persuasive with regard to the Hillman reference and this rejection is withdrawn.

Applicant's arguments with regard to the Fodor rejection are not persuasive. As noted in the new 112, second paragraph rejection, the phrase "at least about" is vague and indefinite, as noted by the Court of Appeals for the Federal Circuit. Given that indefiniteness, it is unclear what is "at least about 20". Therefore, the Fodor rejection is maintained since the 10-mer array includes nucleotides which are "at least about 20" within the indefiniteness of this phrase.

Double Patenting

10. The rejection of claims 38 and 43-46 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,642,370 is withdrawn in view of the terminal disclaimer.

Allowable Subject Matter

11. Claims 41 and 42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. The following is a statement of reasons for the indication of allowable subject matter: The claims are indicated as allowable because claims 41 and 42 are limited to the specific sequences recited and the prior art does not teach these particular sequences.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1637